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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,900	02/24/2004	Eugene R. Cooper	029318-1003	1015

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EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
04/10/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,900	COOPER ET AL.	
	Examiner	Art Unit	
	SUSAN TRAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 February 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-3,6,26-32,35,50-52,55,65,66 and 101-103* is/are pending in the application.

5a) Of the above claim(s) *26-32 and 35* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-3,6,50-52,55,65,66 and 101-103* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

Claims 1-3, 6, 50-52, 55, 65-67 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Struengmann et al. WO 99/09988 A1, in view of Liversidge et al. WO 93/25190 A1, and Desai et al. WO 01/45706 A1 or Courteille et al. US 5,384,124.

This rejection has been withdrawn in view of Applicant's Amendment filed 02/29/12.

Claims 1-3, 6, 50-52, 55, 65-67 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Struengmann et al. WO 99/09988 A1, in view of Liversidge et al. WO 93/25190 A1.

Struengmann teaches a pharmaceutical composition comprising micronized meloxicam with suitable additive such as microcrystalline cellulose and/or surfactant and/or co-solvent (page 3; and examples). Surfactant is disclosed at page 4, last paragraph bridging page 5. Co-solvent includes propylene glycol, polyethylene glycol, glycerol and ethanol (page 3, last paragraph). The obtained meloxicam is then incorporated into dosage forms suitable for oral and parenteral administration (page 5, paragraphs 35).

Struengmann does not expressly teach the particle diameter of the micronized meloxicam. However, one of ordinary skill in the art would have been motivated to, by routine experiment optimize the particle size with the expectation of at least similar

results. This is because it is known in the art to reduce particle size of a drug to obtain a higher bioavailability of said drug. Liversidge teaches a process of preparing nanoparticulate drug substances comprising the steps of dispersing a crystalline drug in a liquid dispersion medium containing a surface modifier, and subjecting the premix to mechanical means to reduce the particles size of the drug substance to less than 400 nm (pages 7-10). Drug includes water-insoluble drug substance such as analgesic and NSAID substances including oxicam (page 3). Surface modifier includes nonionic, anionic, organic, inorganic excipients, and mixture of two or more (pages 5-6). Surface modifier includes polyvinyl pyrrolidone (page 6). Liversidge further teaches the surface modifier is adsorbed on the surface of the drug substance, but the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages (page 6, lines 25-31). Liversidge also teaches the nanoparticles are combined with pharmaceutically acceptable carrier suitable for parenteral injection (page 11, lines 29-35).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the meloxicam composition of Struengmann to obtain a nanoparticulate meloxicam composition in view of the teachings of Liversidge. This is because Liversidge teaches a nanoparticulate composition that exhibits unexpectedly rapid onset (bioavailability) (page 12, lines 11-14), because Liversidge teaches a process suitable for a wide variety of NSAIDs including oxicam, because Struengmann teaches the desirability for obtaining a composition with high bioavailability, and

because Struengmann teaches reducing particle size of meloxicam by micronisation (page 3, last paragraph; page 10; and examples).

It is noted that Struengmann does not explicitly teach the claimed properties such as the C_{max} values. However, it would have been obvious to one of ordinary skill in the art to, by routine experimentation obtain the C_{max} value that falls within the claimed range, because Liversidge teaches nanoparticulate having the claimed particle size in a dispersion for parenteral injection exhibits the claimed C_{max} value, e.g., 187 µg/mL (page 16).

Claims 1-3, 6, 50-52, 55, 65-67, 87 and 101-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Struengmann et al. WO 99/09988 A1, in view of Liversidge et al. WO 9325190 A1, and Cunningham et al. US 20040018242 A1.

Struengmann is relied upon for the reasons stated above. Struengmann does not expressly teach the claimed surface stabilizer such as sodium deoxycholate.

Cunningham teaches a nanoparticulate formulation comprising one or more surface stabilizer such as sodium deoxycholate and polyvinylpyrrolidone (paragraphs 106-107; claims 13, 48 and 69). Cunningham further teaches that surface stabilizers useful herein do not chemically react with the drug particle, and that the individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages (paragraph 0094).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include sodium deoxycholate as a surface stabilizer in view of

the teachings of Cunningham. This is because Cunningham teaches the use of sodium deoxycholate and/or polyvinylpyrrolidone as a surface stabilizer is known in the art, and because Struengmann teaches the desirability for including surfactant such as polyvinylpyrrolidone.

Response to Arguments

Applicant's arguments filed 02/29/12 have been fully considered but they are not persuasive.

The Declaration under 37 CFR 1.132 filed 02/29/12 is insufficient to overcome the 103(a) rejections as set forth in the last Office action. Since Applicant's Remarks referred to the Declaration, the Examiner chose to reply to the Remarks and the Declaration concurrently.

Applicant pointed out that the Declaration under 37 C.F.R. 1.132 executed by Dr. Gary Liversidge ("the Liversidge Declaration II") specifically attests that: (a) not all active agents can be made into stable nanoparticulate active agent compositions; and (b) not all nanoparticulate active agent compositions can achieve improved bioavailability. More particularly, the Liversidge Declaration II teaches that even when a functional equivalent was successfully made into a nanoparticulate active agent formulation, another active agent in the same functional group could not be obtained. See the Liversidge Declaration II, ¶¶ 4-16. Moreover, the Liversidge Declaration II also teaches that certain active agents, such as orlistat, cannot be made into stable nanoparticulate

active agent compositions despite numerous attempts. *Id.*, ¶¶ 17-20. Furthermore, the Liversidge Declaration II teaches that even if a nanoparticulate active agent composition can be made, there is a lack of predictability regarding whether the nanoparticulate active agent composition will result in improved bioavailability of the component active agent. *Id.*, ¶¶ 25-28. Accordingly, the Liversidge Declaration II provides data and analysis refuting the

Examiner's incorrect presumptions regarding the predictability of making nanoparticulate active agent compositions as well as predicting the properties of such nanoparticulate active agent compositions.

However, Applicant's arguments with respect to the bioavailability are not persuasive for the following reasons:

1) Struengmann teaches an improved bioavailability meloxicam composition (see Struengmann's abstract);

2) Struengmann teaches the use of a dissolution improving agent to improve solubility, thus, improve bioavailability (see abstract and page 3, 3rd and last paragraphs); and

3) Struengmann teaches a micronized meloxicam (page 4, 1st paragraph).

Accordingly, Struengmann teaches the claimed composition. The only deficient in Struengmann's teachings is the size of the micronized particle.

Applicant argues that the combined teachings of the cited references fail to teach the small meloxicam particle size of less than 200 nm in combination with a dosage

form for intravenous injection. Furthermore, the cited references disclose a laundry list of surface stabilizers but fail to identify the specific surface stabilizers of the claimed invention as being preferred to other options. Therefore, in the absence of any teachings from the cited art, the Examiner has failed to articulate why the skilled artisan would have selected Applicants' claimed dosage form for intravenous injection, and the claimed specific surface stabilizers, for the nanoparticulate meloxicam composition. The Examiner could have only reached her rejection based on impermissible hindsight, informed by Applicants' own invention.

However, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicant's attention is called to Liversidge at page 11, lines 29-35 for the teaching of an injection composition comprising the nanoparticles combined with pharmaceutically acceptable carrier (page 11, lines 29-35).

Applicant alleged that as demonstrated by the Liversidge Declaration II, all commercial meloxicam formulations approved by the FDA are in oral dosage forms (tablet or oral suspension). See ¶29. The oral dosage forms of meloxicam have the

undesired side effect of gastrointestinal irritation. In fact, this side effect associated with the oral dosage form is so serious that the FDA requires the package label of meloxicam to carry a black box warning. Id., ¶30. Additionally, an intravenous dosage form having fast onset is highly desirable, particularly for a pain reliever such as meloxicam, and particularly for a very young patient population. Id., ¶32 and 38. Therefore, there was a need to develop an injectable formulation of meloxicam. Id., ¶31. However, it was difficult to obtain an intravenous meloxicam dosage form because meloxicam is poorly water soluble and a formulation containing large meloxicam particles is not suitable for intravenous injection. It was surprising that the claimed invention achieved the unexpected results of obtaining an intravenous nanoparticulate meloxicam formulation, which achieves the same or improved plasma concentration of meloxicam but in a much shorter time period in comparison to the commercial oral dosage form of meloxicam. Id., ¶¶33-38. This is not taught or suggested by the cited art. As such, withdrawal of this ground for rejection is respectfully requested.

However, in response to Applicant's arguments, Applicant's attention is called to page 5, 2nd paragraph, where Struengmann teaches meloxicam having improved solubility for parenteral administration.

Applicant argues that the teachings of Struengmann and Liversidge are discussed *supra*. Cunningham is cited for the alleged teaching of using sodium deoxycholate as a surface stabilizer for the claimed nanoparticulate meloxicam composition. However, the Examiner has failed to articulate why the skilled artisan

would have included sodium deoxycholate as a surface stabilizer in view of Cunningham's teaching that sodium deoxycholate is used as a surface stabilizer for a nanoparticulate nystatin composition. Specifically, nystatin is a polyene antimycotic useful in treating fungal infection. As
disclosed by Cunningham, some "novel surface stabilizers...were selected [for the nanoparticulate nystatin composition] based on their potential bioadhesive or antimicrobial properties." *See* page 14, paragraph [0178]. In other words, one skilled in the art would have understood that the selection of these surface stabilizers was tailored to the specific active agent, nystatin. Cunningham further discloses that sodium deoxycholate was selected due to its unique property, i.e., "used as solubilizer in polyene formulations." *Id.*, Table 2. In contrast, meloxicam of the claimed invention is an entirely different active agent from nystatin. The Examiner has failed to articulate why sodium deoxycholate would have been selected as a surface stabilizer for meloxicam, an active agent that is NOT a polyene, when Cunningham discloses the use of sodium deoxycholate as a solubilizer in polyene formulations. Additionally, Example 4 of Cunningham demonstrates that sodium deoxycholate may have an adverse effect on the minimum inhibitory concentration (MIC) of a nanoparticulate nystatin composition using sodium deoxycholate as a surface stabilizer in comparison to other nanoparticulate nystatin compositions using other surface stabilizers. *See* page 15, paragraph
[0189] ("with the exception of the Na Deoxycholate-stabilized sample of nanoparticulate nystatin, none of the milled formulations exhibited any significant differences in MIC,

and

surprisingly, were more active than unmilled nystatin material.") As such, the skilled artisan would have understood that there was some uncertainty regarding the effectiveness of a nanoparticulate nystatin composition comprising sodium deoxycholate as a surface stabilizer, as the use of a sodium deoxycholate was found to potentially adversely affect the MIC of the nanoparticulate nystatin composition.

However, in response to applicant's arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Cunningham is cited solely for the teachings of sodium deoxycholate as a surface stabilizer.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1615